EDITORIAL COMMENT†

ISO-ANTIGENIC THRESHOLD

Recent attempts to explain erythroblastosin foetalis [1] and puerperal eclampsia [2] as results of reactions between fetal isoantigens and maternal iso-antibodies, render Lewis' [3] current studies of the immunologic properties of cerebral iso-haptens of pertinent clinical interest.

Following the demonstration that lens proteins are alien to other tissues of the animal body, numerous other organ-specific and potentially iso-antigenic proteins were described, prominent among them being: thyroglobulin,[4] fibrinogen [5] and casein.[6] It was shown that each of these is iso-antigenic in rabbits, and will give rise to specific iso-antibodies if repeatedly injected in sufficiently large doses. Interest in organ-specific antigens was heightened by the subsequent discovery that certain organ-specific lipoids and carbohydrates form an essential part of cytoplasm and may determine or modify organ specificity. It was shown by Witebsky,[7] for example, that alien brain emulsions injected into rabbits gave rise to brain-specific antibodies, reacting with a wide range of animal brains, including the brains of rabbits. Rabbits, therefore, are capable of forming antibodies against their own nerve cells, in the same way that they can produce anti-lens precipitins of sufficiently high titer to cause allergic reactions with their own eye tissues.[8]

Witebsky found that the organ-specific determinant common to all brains is an alcohol-extractable lipoid. Injected by itself this brain lipoid is apparently non-antigenic. When tested by routine in vitro methods, however, the lipoid gives specific complement-deviation reactions with anti-brain serums. The lipoid is, therefore, classified as an "incomplete antigen", or "hapten". Lewis [9] was able to demonstrate the same brain lipoid in the testicle, suggesting the possibility that an autogenous anti-testicular immunity may cause secondary functional or anatomical changes in the nervous system.

These earlier studies of cerebral haptens were made with antiserums prepared by injecting rabbits with alien brain emulsions. The active fraction in this heterologous material presumably consists of lipoidal haptens in loose chemical combination with the brain proteins. This alien protein "carrier" is apparently an essential part of the complete antigen, since the same lipoids in normal combination with homologous brain proteins are non-antigenic. This conclusion was confirmed by Lewis, who found that rabbit brain lipoids can be rendered fully iso-antigenic by adsorption on horse proteins. The anti-horse-anti-brain rabbit serum thus obtained will differentiate sharply between the extracted lipoids of various organs: liver, kidney, heart, lungs and spleen giving negative complement-fixation reactions, while both brain and testicular lipoids give positive reactions.

If we should apply this law of hapten antigenicity to the currently controversial question of the immuno-pathology of pregnancy, it would be necessary to assume that in addition to the giving off of organ-specific fetal haptens, there must be a local production or formation of alien or denatured fetal proteins to serve as the necessary hapten-carriers. Theoretically, without this denatured protein carrier the fetal haptens would not stimulate the production of maternal antibodies. The necessity for a denatured protein carrier has been largely overlooked by recent clinical investigators, who have ignored the fact that the so-called A, B, O, and Rh "agglutinogins" are in reality incomplete antigens or haptens.[10]

Clinicians, however, will find an even more important challenge to their conventional logic in Lewis' emphasis on the normal metabolic utilization or homologization [11] of iso-antigens by the reticulo-endothelial cells and other fixed tissues. Fibrinogen is a normal constituent of the circulating blood, while thyroglobulin and casein are probably often given off into the blood stream. All three are known to be iso-antigenic. Nevertheless there is no conclusive evidence that under normal conditions they stimulate the production of iso-antibodies. There is evidently a very effective biochemical mechanism for the hydrolysis, utilization, or homologization of these organ-specific substances. Only under some unknown conditions of fixed-tissue deficiency is iso-antibody production found necessary. Duke,[12] for example, reports one such case, a lactating mother who suffered from allergic reactions when she weaned her child, and in whose blood there were subsequently demonstrated specific antibodies reacting with human casein, but giving negative reactions with cow's milk.

If one should apply the same theory to the currently controversial problem of the iso-antibodies of pregnancy, one would conclude that erythroblastosis foetalis and puerperal eclampsia are presumably not primarily the result of the formation and liberation of fetal isoantigens, but essentially the result of some unknown lowering of the normal destruction of these fetal iro-antigens by maternal tissues, a lowered maternal tissue defense. Such a basic maternal tissue deficiency might conceivably be corrected by appropriate dieting methods.

Lewis has rendered a distinct service to clinical science by emphasizing this most promising field of basic immunochemical research.

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† This department of CALIFORNIA AND WESTERN MEDICINE presents editorial comments by contributing members on items of medical progress, science and practice, and on topics from recent medical books or journals. An invitation is extended to all members of the California Medical Association to submit brief editorial discussions suitable for publication in this department. No presentation should be over five hundred words in length.

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A POSSIBLE CLUE FOR CAUSE OF PLANE CRASHES

A possible clue to one of the factors that may have played a part in some of the recent airplane crashes, the cause of which has mystified investigators, is suggested by C. C. Bunch, Ph.D., St. Louis.

In his discussion of "The Problem of Deafness in Aviators," Dr. Bunch says: "Newspaper accounts of the investigations of recent airplane accidents do not mention the hearing ability of the pilots involved. The reports of the circumstances of several accidents lead one to think that in certain instances the pilots were not following the radio beam. In that at Salt Lake City the newspaper account stated that the plane was approaching the landing field on the radio beam. A few moments later the pilot turned off his course. A storm was in progress at the time. In the recent Chicago accident it was reported that the pilot was attempting to land on the wrong runway. A snow storm was in progress.

"As in the case of the graduate student whose audiogram is recorded [in a chart in the article], the pilot may not be aware of any hearing loss at all. On the other hand, if he did know of it but was unaware of its significance in his profession, it would be human nature for him to attempt to conceal it. These problems may be solved only by frequent accurate audiometric tests by competent examiners."

In his comment on the general problems presented by the subject, Dr. Bunch says that blacksmiths' deafness has been known since 1830 and that as the steel industry developed this peculiar form of deafness became sufficiently well known to be called boilermakers' deafness.

"According to the best information available," he continues, "the noise in a boiler shop reaches an intensity of level of about 100 decibels and that from an airplane motor about 110 decibels. If continuous exposure to the noise in a boiler shop results in diminished hearing, it is logical to expect that . . . the louder noise [of airplane motors] will produce hearing losses more frequently and more quickly. . . .

"There is no evidence that the ordinary use of the telephone will result in deafness. . . .

"The public knows that the pilots of modern planes are at times in communication with the radio stations located at landing fields. . . . Whether the conditions under which he must use his radio would result in diminished hearing is not known to the interested public. . . . Padden, discussing Wright's paper entitled 'Medical Supervision of Air Lines,' made these significant remarks:

" 'The increasing importance of radio and radio beams finds a condition of static ears occurring in quite a number of pilots. It requires intense concentration for a pilot to listen four hours to *ta-ti-ta.* Occasionally I sit up front and stick the ear phones on and I don't wonder they get static ears with electrical storms, etc. I think I'd have static ears in one trip.'

"Just what he meant by 'static ears' is difficult to understand. It is possible that the static which occurs during thunder storms might cause temporary or permanent hearing losses which would adversely affect the pilot's efficiency?

'Nearly every one has had the unpleasant experience of attempting to use a telephone located in a noisy place. The pilot must use his radio in the presence of the roar of the motors of his ship, and in order to hear it he must turn it on louder than would ordinarily be necessary. Unfortunately, as he increases the loudness of his radio signal he must also increase the loudness of the static, thus creating a grave situation to say the least. . . ."

In summarizing his discussion, Dr. Bunch says:

"It is not scientific to assume that hearing losses which have been found in those who are employed in one industry will be found in those employed in another unless a common cause exists. In this instance it appears that a common cause, that is, excessively loud noise, exists. The following conclusions appear to be definite but cannot be proved without more complete investigation:

"1. The best evidence available indicates that the loud noises of airplanes and airplane motors often cause definite hearing losses in pilots.

"2. All pilots are not affected to the same degree.

"3. The hearing loss most frequently encountered in those who have been exposed to loud noises is for tones near c-4 (2048 double vibrations) and c-5 (4096 double vibrations). As the loss progresses with continued exposure, the acuity for tones of lower pitch is also affected.

"4. Pilots who have decreased acuity for tones near c-3 (1024 double vibrations) will have difficulty in understanding certain words over the radio and may not be able to understand exact landing instructions.

"5. If the radio guide beam has a frequency near c-3 (1024 double vibrations) pilots with [decreased] hearing losses [for tones near c-3] can follow it only when they keep their radios tuned on louder than is ordinarily necessary.

"6. Lightning-created static in the ears of